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Palladium(0)-catalyzed asymmetric C(sp³)-H arylation using a chiral binol-derived phosphate and an achiral ligand†

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The first efficient palladium(0)-catalyzed enantioselective C(sp³)-H activation reaction using a catalytic chiral base and an achiral phosphine ligand is reported. Fine-tuning the binol-derived phosphoric acid pre-catalyst and the reaction conditions was found to be crucial to achieve high levels of enantioselectivity for a variety of indoline products containing both tri- and tetrasubstituted stereocenters.

Introduction

Transition-metal catalysis has developed as a powerful tool to activate otherwise unreactive C(sp³)-H bonds and create a variety of carbon-carbon and carbon-heteroatom bonds.^{1,2} In this context, our group³ as well as others⁴ have reported the construction of a diverse array of fused carbocycles and heterocycles *via* intramolecular palladium(0)-catalyzed arylation of unactivated C(sp³)-H bonds from aryl halides. In the last five years, enantioselective versions of these reactions have been disclosed. In particular, the groups of Kündig,⁵ Kagan,⁶ and Cramer^{7a} reported the highly enantioselective construction of (fused) indolines using chiral *N*-heterocyclic carbene or phosphine ligands (Table 1, entry 1). In parallel, we have reported the diastereo- and enantioselective synthesis of (fused) indanes containing up to three adjacent stereocenters by using chiral Binepine ligands.⁸ Computational mechanistic studies indicated that the C-H bond cleavage occurs through proton abstraction by the coordinated base, usually either a carbonate or an *in situ* generated carboxylate (concerted metalation-deprotonation mechanism).^{3b,c,4f,h,5c,d,9,10} In this scenario, not only the ancillary ligand, but also the base should be able to interact with the substrate *via* non-covalent bonding, and hence induce stereoselective C-H bond cleavage. The possibility that enantioselectivity can be achieved solely using a chiral base was already explored in the above-mentioned work by Kagan⁶ and Cramer.^{7a} Indeed, the former observed an e.r. of 65 : 35 in the presence of 50 mol% of Boc-valine in the absence of an ancillary ligand (entry 2), whereas the latter reported an e.r. of 71 : 29 using a chiral tetralinecarboxylic acid and an achiral NHC

ligand (entry 3).^{11,12} In both cases the indoline product was, however, obtained in low yield.

Encouraged by these precedents, we looked for a suitable chiral Brønsted acid pre-catalyst, which upon *in situ* deprotonation with a stoichiometric inorganic base, would allow the achievement of both efficiency and high enantioselectivity. Our attention turned toward binol-derived phosphoric acids (BPAs), which are readily available, and have proven to be competent stereochemical inducers in other types of reactions involving cooperative catalysis with Pd complexes,^{13,14} and, as shown recently by Duan and co-workers, in Pd^{II}-catalyzed directed asymmetric C(sp³)-H arylation.¹⁵ When the current work was in progress, the same group reported two examples of Pd⁰-catalyzed enantioselective synthesis of indolines using the simplest BPA, devoid of substituents at the 3,3'-positions, with a moderate e.r. and yield.¹⁶

Herein, we show that high levels of enantioselectivity and efficiency can be obtained through the careful choice of BPA substituents and optimization of reaction conditions (entry 4).

Results and discussion

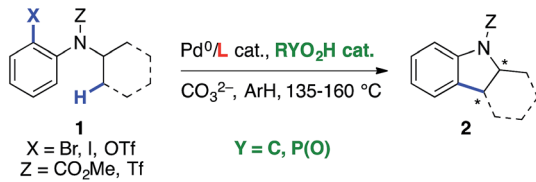
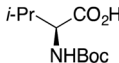
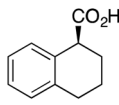
We set out to explore the asymmetric C-H arylation of prototypical substrate **1a** bearing enantiotopic methyl groups (Table 2). The well-defined Pd(PCy₃)₂ complex (5 mol%) was initially chosen as catalyst to minimize the effect of additional ancillary ligands or anions. In order to have a blueprint for the design of an efficient BPA catalyst, we considered the putative κ²-coordinated intermediate^{13g} derived from 3,3'-disubstituted BPAs, which would undergo C-H activation *via* a phosphate-induced CMD mechanism (Fig. 1, left). In this crude model, a 3'-aryl substituent would sit below the *N*-isopropyl and CO₂Me groups of the substrate, thereby enabling non-covalent interactions. Fig. 1 (right) shows the DFT-optimized structure of the κ² complex with the optimal (*vide infra*) BPA **3g**, which provides a more accurate picture. According to this model, the modulation of the steric and/or electronic properties of the 3,3'-aryl

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† Electronic supplementary information (ESI) available: Full optimization tables, procedural, spectral and X-ray crystallographic (CIF) data, and DFT calculations. CCDC 1486752 and 1486753. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc04006c



Table 1 Chiral ligand- vs. chiral base-catalyzed asymmetric C(sp³)-H arylation^a

				
Entry	L	Brønsted acid RYO ₂ H	e.r. (yield)	ref.
1	Chiral NHC or phosphine	Achiral RCO ₂ H	Up to 99 : 1 Up to 97 : 3 Up to 98 : 2	Kündig ⁵ Kagan ⁶ Cramer ^{7a}
2	None	 (50 mol%)	65 : 35 (Traces)	Kagan ⁶
3	IPr	 (25 mol%)	71 : 29 (20%)	Cramer ^{7a}
4	PCy ₃	3,3'-CF ₃ Ph-BPA	Up to 98 : 2	<i>This work</i>

^a IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene; BPA = binol-derived phosphoric acid.

substituents could allow the introduction of enantioselectivity by discriminating the two enantiotopic methyl groups of the *N*-isopropyl residue.

Following this hypothesis, an array of 3,3'-disubstituted BPAs were synthesized from (*R*)-binol according to literature procedures¹⁷ and were tested as catalysts (10 mol%) in combination with stoichiometric cesium carbonate in xylenes. The most representative results are shown in Table 2.¹⁸ The nature of the 3,3'-substituents was indeed found to be crucial, with methyl (entry 1), phenyl (entry 2) or extended aryl groups (entries 3–4) leading to very low levels of enantioselectivity.

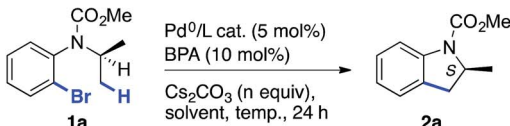
meta-Substituents on the 3,3'-phenyl rings led to the first interesting results (entries 5–8). The highest e.r. (80 : 20) was obtained with commercially available BPA **3g** bearing *meta*-CF₃ substituents (entry 7),¹⁹ which performed much better than the sterically comparable isopropyl (entry 6) or likewise electron-withdrawing nitro (entry 8) groups. As shown with the partially hydrogenated analogue **3g**-[H₈] (entry 9), the dihedral angle of the binaphthyl system seems to be a critical factor as well. Decreasing the temperature to 120 °C enabled a significant increase in the e.r., albeit at the expense of the yield (entry 10, compared with entry 7). We hypothesized that the low solubility of cesium carbonate in xylenes and the resulting incomplete deprotonation of the BPA was responsible for the observed low reactivity at 120 °C. Gratifyingly, increasing the amount of Cs₂CO₃ to 3 equiv. allowed an increase in the yield to 56% (entry 11). Modulating the acidity of the BPA²⁰ by synthesizing phosphoramides **3i**–**j** was met with little success (entries 12–13). In contrast, a major improvement was found when using DME as the solvent. Moreover, the addition of 4 Å molecular sieves

proved beneficial, leading to compound **2a** in excellent yield and e.r. (entry 14). It is worth noting that a slow but significant background racemic reaction occurred with cesium carbonate alone, in the absence of BPA (entry 15). Among all of the stoichiometric bases tested in combination with catalytic acid **3g**, cesium carbonate proved to be optimal. Finally, the effect of the ancillary ligand was investigated in combination with Pd₂dba₃ (entries 16–20). No reaction occurred without phosphine ligand (entry 16), and PCy₃ furnished the highest reactivity (entry 17) among the tested monophosphines. It is noteworthy that the *in situ* combination of Pd₂dba₃ and PCy₃ provided the same e.r. as the well-defined Pd(PCy₃)₂ complex, but the latter was found to be a more active catalyst (compare entries 14 and 17). Hence, under optimal conditions, indoline **2a** was obtained in 86% yield and 96 : 4 e.r. (entry 14). The (*S*) absolute configuration of the major enantiomer was ascribed *via* X-ray diffraction analysis of a derivative (*vide infra*). These levels of reactivity and selectivity are comparable to those obtained on the same substrate with the chiral ancillary ligand approach.²¹

The scope and limitations were next studied under these optimized conditions (Scheme 1), starting with reactants bearing a trisubstituted carbon adjacent to the nitrogen atom (R² = H, Scheme 1a). Among the different tested halides (X = Cl, Br, I), the bromide was found to be optimal. Importantly, the reaction could be performed from 1.36 g (5 mmol) of the latter with equal efficiency and stereoselectivity. From the corresponding iodide, the e.r. was similar (96 : 4) but the yield was significantly lower (68%). The chloride was less reactive under the same conditions, and lower yield and e.r. were obtained even at 140 °C. The effect of the nitrogen substituent (R¹) was next



Table 2 Optimization of reaction conditions



3a: Y = OH, R = Me
3b: Y = OH, R = Ph
3c: Y = OH, R = 2-naphthyl
3d: Y = OH, R = 9-phenanthrenyl
3e: Y = OH, R = (3,5-di-Me)Ph
3f: Y = OH, R = (3,5-di-*i*-Pr)Ph
3g: Y = OH, R = (3,5-di-CF₃)Ph
3h: Y = OH, R = (3,5-di-NO₂)Ph
3g-[H₈]: Y = OH, R = (3,5-di-CF₃)Ph
3i: Y = NH₂, R = (3,5-di-CF₃)Ph
3j: Y = NHTf, R = (3,5-di-CF₃)Ph

Entry	BPA	Catalyst ^a	<i>n</i>	Solvent	Temp. (°C)	e.r. of 2a ^b	Yield of 2a ^c (%)
1	3a	Pd(PCy ₃) ₂	1.5	Xylenes	140	52 : 48	80
2	3b	Pd(PCy ₃) ₂	1.5	Xylenes	140	50 : 50	65
3	3c	Pd(PCy ₃) ₂	1.5	Xylenes	140	54 : 46	68
4	3d	Pd(PCy ₃) ₂	1.5	Xylenes	140	52 : 48	71
5	3e	Pd(PCy ₃) ₂	1.5	Xylenes	140	57 : 43	39
6	3f	Pd(PCy ₃) ₂	1.5	Xylenes	140	56 : 44	45
7	3g	Pd(PCy ₃) ₂	1.5	Xylenes	140	80 : 20	50
8	3h	Pd(PCy ₃) ₂	1.5	Xylenes	140	57 : 43	50
9	3g-[H₈]	Pd(PCy ₃) ₂	1.5	Xylenes	140	50 : 50	63
10 ^d	3g	Pd(PCy ₃) ₂	1.5	Xylenes	120	87 : 13	24
11	3g	Pd(PCy ₃) ₂	3	Xylenes	120	84 : 16	56
12	3i	Pd(PCy ₃) ₂	3	Xylenes	120	84 : 16	50
13	3j	Pd(PCy ₃) ₂	3	Xylenes	120	55 : 45	15
14	3g	Pd(PCy ₃) ₂	3	DME ^e	120	96 : 4	86
15	—	Pd(PCy ₃) ₂	3	DME ^e	120	—	29
16	3g	Pd ₂ (dba) ₃	3	DME ^e	120	—	<2 ^f
17	3g	Pd ₂ (dba) ₃ /PCy ₃	3	DME ^e	120	95 : 5	61
18	3g	Pd ₂ (dba) ₃ /PPh ₃	3	DME ^e	120	91 : 9	<20 ^f
19	3g	Pd ₂ (dba) ₃ /PCyp ₃	3	DME ^e	120	97 : 3	24
20	3g	Pd ₂ (dba) ₃ /P(<i>t</i> -Bu) ₂ Me	3	DME ^e	120	97 : 3	<20 ^f

^a 5 mol% Pd(PCy₃)₂ (entries 1–15) or 2.5 mol% Pd₂(dba)₃/10 mol% PR₃ (entries 16–20). ^b Enantiomeric ratio measured *via* HPLC using a chiral stationary phase. ^c Yield of isolated product. ^d Reaction time: 40 h. ^e With 4 Å powdered molecular sieves. ^f Estimated based on GCMS ratio. DME = 1,2-dimethoxyethane.

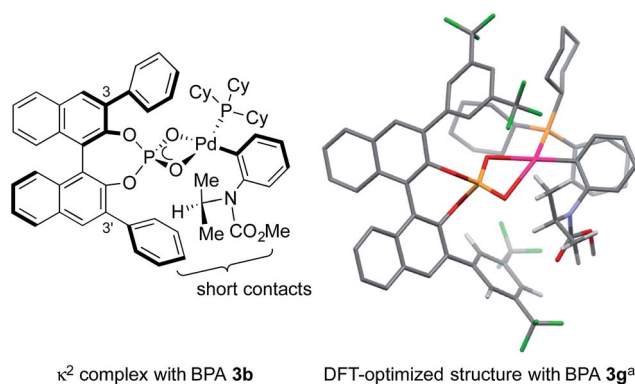


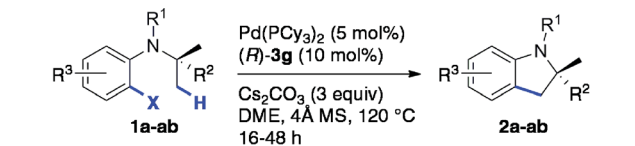
Fig. 1 Structural basis for the design of BPA catalysts. ^aPBE0-D3/Def2SVP, SMD; most H atoms are omitted for clarity.

investigated (indolines **2b–g**). Carbamates were found to be optimal (**2a–d**), whereas other groups gave rise to lower yields (**2f–g**) and enantioselectivities (**2e**, **2g**). This important effect of the nitrogen substituent is consistent with the model described in Fig. 1, which shows the proximity of the CO₂Me group with the 3'-aryl substituent of the BPA.

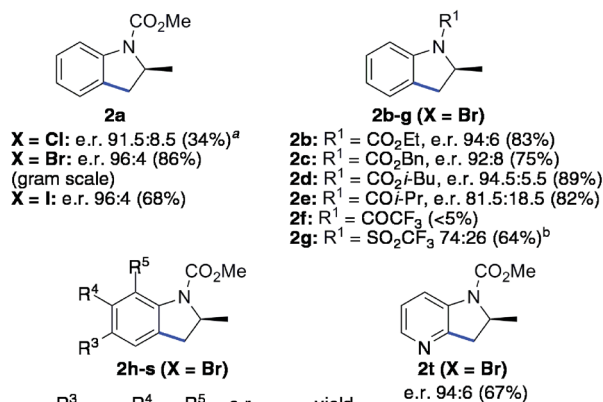
In addition, the reaction was found to tolerate electronically diverse substituents at various positions (R³–R⁵) on the aromatic ring (**2h–s**), including ester (**2k**), cyano (**2l**) and amino (**2o**) groups. High yields and e. r. were obtained for all of the substrates except for those bearing Me or Cl substituents at the C-5 (R³) and C-7 (R⁵) positions of the indoline ring, which seem to be more sensitive. In addition to indolines, azaindoline **2t** was obtained with satisfying yield and stereoselectivity.

So far, both the chiral ligand^{5–7} and the chiral base approaches allow access to scalemic indolines containing a trisubstituted stereocenter. In addition to these compounds, interesting new types of indolines were targeted (Scheme 1b and c). First, indoline **2u** containing a tetrasubstituted stereocenter was obtained with good yield and e.r., despite the more crowded environment of the enantiotopic methyl groups. Interestingly, the carbonyl substituents on the adjacent carbon (**2v**) and nitrogen (**2w**) atoms were found to have a significant impact on both the yield and enantioselectivity, with smaller methoxy-carbonyl groups being optimal (**2u**). Gratifyingly, substituted analogues of **2u** (**2x–z**) were obtained with comparable enantioselectivity. The current method represents a simple enantioselective route to these valuable tetrasubstituted amino acid

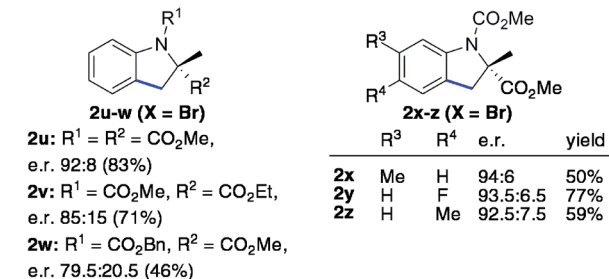




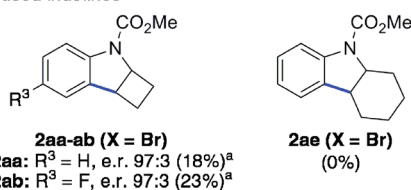
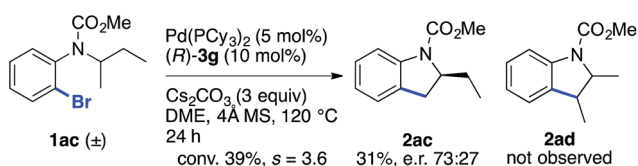
a) indolines with trisubstituted stereocenter



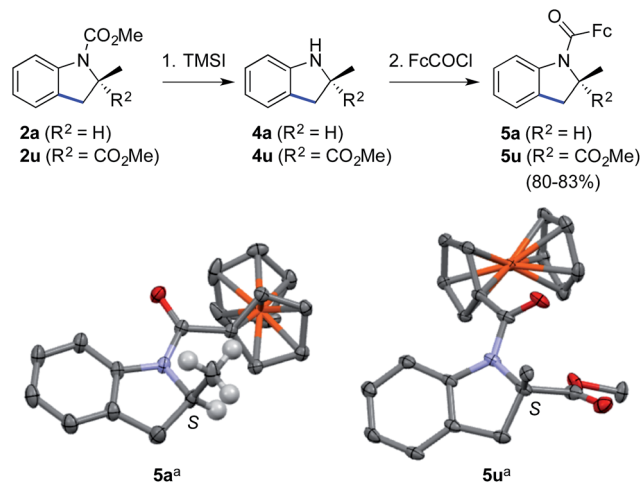
b) indolines with tetrasubstituted stereocenter



c) fused indolines

Scheme 1 Scope and limitations of the enantioselective C(sp³)-H arylation reaction. The shown absolute configurations of the major enantiomers were deduced from those of **2a** and **2u** (see Scheme 3).^a Performed at 140 °C. ^b Performed at 100 °C.

Scheme 2 Study of the kinetic resolution of a racemic substrate.

Scheme 3 Cleavage of the carbamate group and determination of absolute configurations. Reaction conditions: (1) (i) TMSI (10 equiv.), CHCl₃, reflux; (ii) MeOH, reflux (only for **4u**); and (2) for **5a**: FcCOCl (1.1 equiv.), *i*-Pr₂NEt (3 equiv.), 4-dimethylaminopyridine (0.1 equiv.), CH₂Cl₂, 0 → 20 °C, 83% for 2 steps; for **5u**: LiN(SiMe₃)₂ (1.2 equiv.), FcCOCl (1.2 equiv.), THF, -78 → -10 °C, 80% for 2 steps. TMSI = trimethylsilyl iodide; Fc = ferrocene. ^a Thermal ellipsoids at the 30% probability level, most H atoms are omitted for clarity.²⁶

precursors, which does not involve chemical or enzymatic resolution.²²

Various indolines fused to five-, six- and seven-membered rings have been synthesized *via* enantioselective C-H arylation in the presence of chiral ligands.^{5a,c,6,7a} In contrast, a single example of fused indoline-cyclobutane has been reported in its racemic form by Fagnou and co-workers.²³ Using our optimized conditions, compounds **2aa** and **2ab** were obtained with high enantioselectivity (e.r. 97 : 3), albeit in low isolated yield due to significant competing proto-dehalogenation (Scheme 1c). Under the same conditions, the formation of cyclohexane-fused indoline **2ae** was not observed. In contrast, chiral NHC ligands allowed the production of the same product in high yield and enantioselectivity.^{5a} Overall, as shown with compounds **2aa-ab** and **2ae**, the current Pd/PCy₃/BPA catalytic system does not seem to be sufficiently reactive to efficiently activate secondary C-H bonds.

The reaction of racemic substrate **1ac** was also examined, in order to look for a possible kinetic resolution phenomenon (Scheme 2). With the same substrate and using a chiral NHC ligand, Kündig and co-workers observed a regiodivergent behavior, with each enantiomer of **1ac** being transformed into a different enantioenriched product, **2ac** or **2ad**, resulting from the activation of the Me and Et group, respectively.^{5b} Under our standard conditions, we observed only the formation of compound **2ac** arising from the activation of the Me group, and an e.r. of 73 : 27 was measured at 39% conversion (*s* = 3.6).²⁴ Hence, these two different chiral systems show a different behavior, with the chiral BPA giving rise to modest kinetic resolution.

Finally, the methyl carbamate in indolines containing a tri- (**2a**) or tetrasubstituted (**2u**) stereocenter could be cleaved upon



treatment with trimethylsilyl iodide,²⁵ thus leading to valuable scalemic secondary amines **4a** and **4u** (Scheme 3). The latter were derivatized as ferrocenecarboxamides, according to our recently published method,^{8b} to give amides **5a** and **5u** in excellent overall yield. The crystal structures of the corresponding major enantiomers were solved using X-ray diffraction analysis,²⁶ thereby allowing us to independently confirm the *S* configuration of **2a**^{6,27} and to ascribe the *S* configuration for **2u**.¹⁸

Conclusions

In conclusion, we have reported the first highly enantioselective and efficient palladium(0)-catalyzed C(sp³)-H activation reaction using a chiral catalytic base instead of a chiral ancillary ligand. A fine tuning of both the BPA catalyst and the reaction solvent was key to achieve high levels of enantioselectivity for a variety of indoline products containing both tri- and tetra-substituted stereocenters. Further applications of this concept will be reported in due course.

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Notes and references

- Selected reviews: (a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.-Eur. J.*, 2010, **16**, 2654; (b) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (c) H. Li, B.-J. Li and Z.-J. Shi, *Catal. Sci. Technol.*, 2011, **1**, 191; (d) N. Dastbaravardeh, M. Christakakou, M. Haider and M. Schnürch, *Synthesis*, 2014, **46**, 1421; (e) J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 2.
- O. Baudoin, in *Catalytic Transformations via C-H Activation*, ed. J.-Q. Yu, Science of Synthesis, Georg Thieme Verlag KG, Stuttgart-New York, 2015, vol. 2, pp. 37–62.
- Selected examples: (a) O. Baudoin, A. Herrbach and F. Guéritte, *Angew. Chem., Int. Ed.*, 2003, **42**, 5736; (b) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157; (c) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, 2010, **132**, 10706; (d) J. Sofack-Kreutzer, N. Martin, A. Renaudat, R. Jazzar and O. Baudoin, *Angew. Chem., Int. Ed.*, 2012, **51**, 10399; (e) S. Janody, R. Jazzar, A. Comte, P. M. Holstein, J.-P. Vors, M. J. Ford and O. Baudoin, *Chem.-Eur. J.*, 2014, **20**, 11084; (f) D. Dailier, G. Danoun and O. Baudoin, *Angew. Chem., Int. Ed.*, 2015, **54**, 4919; (g) P. M. Holstein, D. Dailier, J. Vantourout, J. Shaya and O. Baudoin, *Angew. Chem., Int. Ed.*, 2016, **55**, 2805.
- For pioneering work: (a) G. Dyker, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1023; (b) G. Dyker, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 103; (c) M. Catellani, E. Motti and S. Ghelli, *Chem. Commun.*, 2000, 2003; other selected references: (d) C.-G. Dong and Q.-S. Hu, *Angew. Chem., Int. Ed.*, 2006, **45**, 2289; (e) H. Ren and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 3462; (f) M. Lafrance, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 14570; (g) T. Watanabe, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2008, **10**, 1759; (h) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 10692; (i) C. Tsukano, M. Okuno and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2012, **51**, 2763; (j) T. Piou, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 11561; (k) J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 4945.
- (a) M. Nakanishi, D. Katayev, C. Besnard and E. P. Kündig, *Angew. Chem., Int. Ed.*, 2011, **50**, 7438; (b) D. Katayev, M. Nakanishi, T. Bürgi and E. P. Kündig, *Chem. Sci.*, 2012, **3**, 1422; (c) E. Larionov, M. Nakanishi, D. Katayev, C. Besnard and E. P. Kündig, *Chem. Sci.*, 2013, **4**, 1995; (d) D. Katayev, E. Larionov, M. Nakanishi, C. Besnard and E. P. Kündig, *Chem.-Eur. J.*, 2014, **20**, 15021.
- S. Anas, A. Cordi and H. B. Kagan, *Chem. Commun.*, 2011, **47**, 11483.
- (a) T. Saget, S. J. Lemouzy and N. Cramer, *Angew. Chem., Int. Ed.*, 2012, **51**, 2238; for the asymmetric synthesis of other fused ring systems, see: (b) T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2012, **51**, 12842; (c) J. Pedroni, M. Boghi, T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9064; (d) J. Pedroni, T. Saget, P. A. Donets and N. Cramer, *Chem. Sci.*, 2015, **6**, 5164; (e) J. Pedroni and N. Cramer, *Angew. Chem., Int. Ed.*, 2015, **54**, 11826.
- (a) N. Martin, C. Pierre, M. Davi, R. Jazzar and O. Baudoin, *Chem.-Eur. J.*, 2012, **18**, 4480; (b) P. M. Holstein, M. Vogler, P. Larini, G. Pilet, E. Clot and O. Baudoin, *ACS Catal.*, 2015, **5**, 4300.
- L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.
- C. E. Kefalidis, O. Baudoin and E. Clot, *Dalton Trans.*, 2010, **39**, 10528.
- In addition, a cooperative effect was demonstrated using a monoprotected *tert*-leucine and a chiral phosphine.^{7a}
- For pioneering work with chiral monoprotected aminoacids in asymmetric Pd^{II}-catalyzed C-H functionalization: (a) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882; for an account: (b) K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927.
- Selected examples: (a) H. Alper and N. Hamel, *J. Am. Chem. Soc.*, 1990, **112**, 2803; (b) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (c) G. Jiang, R. Halder, Y. Fang and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 9752; (d) Z. Chai and T. J. Rainey, *J. Am. Chem. Soc.*, 2012, **134**, 3615; (e) K. Ohmatsu, M. Ito, T. Kunieda and T. Ooi, *Nat. Chem.*, 2012, **4**, 473; (f) S.-Y. Yu, H. Zhang, Y. Gao, L. Mo, S. Wang and Z.-J. Yao, *J. Am. Chem. Soc.*, 2013, **135**, 11402; (g) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma and W. Hu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13356; (h) P.-S. Wang,



- H.-C. Lin, Y.-J. Zhai, Z.-Y. Han and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2014, **53**, 12218; (i) D. Banerjee, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2014, **53**, 13049; (j) T. Jiang, T. Bartholomey, J. Mazuela, J. Willersinn and J.-E. Bäckvall, *Angew. Chem., Int. Ed.*, 2015, **54**, 6024; (k) H. M. Nelson, B. D. Williams, J. Miró and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3213.
- 14 For reviews: (a) R. J. Philipps, G. L. Hamilton and F. D. Toste, *Nat. Chem.*, 2012, **4**, 603; (b) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518; (c) S. M. Inamdar, V. S. Shinde and N. T. Patil, *Org. Biomol. Chem.*, 2015, **13**, 8116.
- 15 S.-B. Yan, S. Zhang and W.-L. Duan, *Org. Lett.*, 2015, **17**, 2458.
- 16 E.r. 75 : 25, 47% yield for indoline **2a**, and e.r. 83.5 : 16.5, 39% yield for indoline **2ae**: S. Zhang, J. Lu, J. Ye and W.-L. Duan, *Chin. J. Org. Chem.*, 2016, **36**, 752.
- 17 (a) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566; (b) D. Uruguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356; review: (c) D. Kampen, C. M. Reisinger and B. List, *Top. Curr. Chem.*, 2009, **291**, 395.
- 18 See the ESI for details.†
- 19 (a) T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.*, 2005, **7**, 2583; (b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann and M. Bolte, *Org. Lett.*, 2005, **7**, 3781.
- 20 K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping and I. Leito, *Angew. Chem., Int. Ed.*, 2013, **52**, 11569.
- 21 With Me-Duphos: 97% yield, e.r. 96.5 : 3.5;⁶ with a chiral NHC: 86% yield, e.r. 95 : 5.^{5b}.
- 22 (a) E. J. Corey, R. J. McCaully and H. S. Sachdev, *J. Am. Chem. Soc.*, 1970, **92**, 2476. For the enantioselective synthesis of tetrasubstituted indolines *via* other approaches: (b) F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu and Q. Cai, *J. Am. Chem. Soc.*, 2012, **134**, 14326; (c) Q. Cai and F. Zhou, *Synlett*, 2013, 408; (d) J. Liu, J. Yan, D. Qin and Q. Cai, *Synthesis*, 2014, 1917; (e) Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, *J. Am. Chem. Soc.*, 2014, **136**, 3732.
- 23 S. Rousseaux, B. Liégault and K. Fagnou, *Chem. Sci.*, 2012, **3**, 244.
- 24 Selectivity factor calculated as $s = \log[1 - c(1 + ee_{2ac})]/\log[1 - c(1 - ee_{2ac})]$, where c = conversion of **1ac**.
- 25 M. E. Jung and M. A. Lyster, *J. Chem. Soc., Chem. Commun.*, 1978, 315.
- 26 CCDC 1486752 (**5a**) and 1486753 (**5u**) contain the supplementary crystallographic data for this paper.†
- 27 K. M. Bertini Gross, Y. M. Jun and P. Beak, *J. Org. Chem.*, 1997, **62**, 7679.

